

**REMARKS**

Applicants note that in several responses filed in this case, the application has been incorrectly titled. In accordance with the Preliminary Amendment filed with the Application on August 28, 2001, the application is now entitled "DETECTION OF TARGET SEQUENCES BY CLEAVAGE OF NON-TARGET NUCLEIC ACIDS", as shown on the first page of this response.

Applicants note with appreciation that the previous objection to Claim 84 and the previous rejections under 35 U.S.C. § 112 have been removed.

Claims 71-94 are pending in the present case. Claims 81 and 85 are canceled herein, and Claims 71, 82, and 86 have been amended. Applicants note that all amendments of Claims presented herein are made without acquiescing to any of the Examiner's arguments or rejections, and are made solely for the purpose of expediting the patent application process in a manner consistent with the PTO's Patent Business Goals (PBG),<sup>1</sup> and without waiving the right to prosecute the unamended Claims or similar Claims in the future.

In the present Office Action the Examiner has made number of objections and rejections, as follows.

1. A number of objections to the drawings were raised by the Draftsperson in a Notice mailed with the prior Office Action on June 17, 2003. The Examiner requires proposed corrected drawings to be filed with the present Response.
2. Claims 71-81, 87, 88 and 92-94 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 4,994,368 to Goodman, *et al.*
3. The Claims stand rejected under 35 U.S.C. § 103. In particular:
  - i. Claims 71-81, 87, 88, and 92-94 stand rejected under 35 U.S.C. § 103 as allegedly being unpatentable over U.S. Patent No. 4,994,368 to Goodman, *et al.*, in view of U.S. Patent No. 5,994,056 to Higuchi, *et al.*

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<sup>1</sup> 65 Fed. Reg. 54603 (Sept. 8, 2000).

- ii. Claims 71-88 and 92-94 stand rejected under 35 U.S.C. § 103 as allegedly being unpatentable over U.S. Patent 4,994,368 to Goodman, *et al.*, in view of U.S. Patent No. 5,994,056 to Higuchi, *et al.*, and further in view of U.S. Patent No. 5,210,015 to Gelfand, *et al.*
- iii. Claims 71-94 stand rejected under 35 U.S.C. § 103 as allegedly being unpatentable over U.S. Patent 4,994,368 to Goodman, *et al.*, in view of U.S. Patent No. 5,994,056 to Higuchi, *et al.*, further in view of U.S. Patent No. 5,210,015 to Gelfand, *et al.*, and U.S. Patent No. 4,935,357 to Szybalski.

These rejections and objections will be addressed in the order presented.

**1. SUBMISSION OF DRAWINGS**

The Examiner has noted that the Draftsperson has made a number of objections to the drawings. A complete set of replacement drawings is provided herewith. Applicants have provided the most accurate representation of these figures that is available. These same figures have previously issued in U.S. Patent Nos. 5,843,669 on December 1, 1998, and 6,372,424 on April 16, 2002. Applicants respectfully request that these objections be removed.

**2. THE CLAIMS ARE NOT ANTICIPATED**

Claims 71-81, 87, 88 and 92-94 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 4,994,368 to Goodman, *et al.* (hereinafter Goodman).

Claim 71 as amended teaches the use of an enzyme comprising a 5' nuclease in the cleavage of each of the first and the second cleavage complexes. All other claims depend from Claim 71, either directly or indirectly, and therefore comprise the same limitations. This element was previously found in Claim 85, now canceled and as such is not new matter. Further, Claim 85, which was not rejected as being anticipated by Goodman. As such, it appears that there should be no disagreement that the rejection should be withdrawn in view of this amendment.

The present invention is additionally distinct from Goodman. In addition to failing to teach the use of an enzyme comprising a 5' nuclease for cleavage in the disclosed amplification

assay, Goodman does not teach the liberation of a 5' portion of a first oligonucleotide by cleavage with an enzyme comprising a 5' nuclease and the use of the liberated 5' portion to form a second complex with a third oligonucleotide, such that the second complex is also cleaved by an enzyme comprising a 5' nuclease.

A claim is not anticipated by a prior art reference when that reference fails to describe each and every element as set forth in the contested claim. *Verdegall Bros. v. Union Oil Co. of California*, 814 F.2d 628 (Fed. Cir. 1987). Goodman fails to teach the elements of the present claims, and thus cannot anticipate the claimed invention. Accordingly, Applicants respectfully request that this rejection be removed.

### **3. THE CLAIMS ARE NOT OBVIOUS**

Claims 71-81, 87, 88, and 92-94 stand rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Goodman, in view of U.S. Patent No. 5,994,056 to Higuchi, *et al.* (hereinafter Higuchi). With the reasoning set forth in the Office Action mailed June 17, 2003, and reiterated in the present Office Action, the Examiner argues that “it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to modify the method of nucleic acid cleavage and nucleic acid detection by fluorescence of Goodman *et al.* with the alternative method of detection by fluorescence quenching as taught by Higuchi.” Office Action of 6/17/03, pg. 7. As noted above, the claims as amended teach the use of an enzyme comprising a 5' nuclease in the cleavage of each of the first and the second cleavage complexes.

Goodman does not teach the use of an enzyme comprising a 5' nuclease for cleavage in the disclosed amplification assay. Further, Goodman does not teach the liberation of a 5' portion of a first oligonucleotide in a complex by cleavage with an enzyme comprising a 5' nuclease, and the use of the liberated 5' portion to form a second complex with a third oligonucleotide, wherein said second complex is also cleaved by an enzyme comprising a 5' nuclease. Combination with the fluorescence detection methods of Higuchi does not cure this deficiency. This combination of references fails to teach or suggest the elements of the presently claimed invention and, as such, the presently claimed invention is nonobvious in view of these references. Applicants therefore respectfully request that these rejections be removed.

The Examiner makes a further combination of these references with Gelfand. Claims 71-88 and 92-94 stand rejected under 35 U.S.C. § 103 as being allegedly being unpatentable over

Goodman in view of Higuchi and further in view of U.S. Patent No. 5,210,015 to Gelfand, *et al.* (hereinafter Gelfand). In particular, the Examiner argues that “it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to modify the method of nucleic acid cleavage and nucleic acid detection by fluorescence quenching of Goodman *et al.* and Higuchi *et al.* with the 5' nuclease enzyme which is comprised in a thermostable DNA polymerase from an organism of the genus *Thermus* used in a method of cleaving a first nucleic acid which has been hybridized to a target nucleic acid as taught by Gelfand *et al.* for the expected benefit of maintaining enzyme activity at the higher temperatures required for hybridization of nucleic acids.” Office Action of 6/17/ 03, pg. 8. As noted above, Goodman does not teach a method comprising the liberation of a 5' portion of a first oligonucleotide by cleavage with an enzyme comprising a 5' nuclease and the use of the liberated 5' portion to form a second complex with a third oligonucleotide, wherein said second complex is also cleaved by an enzyme comprising a 5' nuclease, and combination with Higuchi does not cure this deficiency.

The further combination with Gelfand still fails to cure this deficiency. As noted by the Examiner in the Office Action of 6/17/03 (at page 8), Gelfand teaches the cleavage of a nucleic acid using a thermostable polymerase comprising a 5' nuclease. Gelfand does NOT teach the liberation of a 5' portion of a first oligonucleotide by cleavage with an enzyme comprising a 5' nuclease, and the use of the liberated 5' portion to form a second complex with a third oligonucleotide, wherein said second complex is also cleaved by an enzyme comprising a 5' nuclease. Neither Goodman nor Gelfand provide any teachings to on how to combine the 5' nucleases of Gelfand with the restriction enzyme-based amplification assay of Goodman so as to approximate the steps of the presently claimed invention. In particular, neither reference provides any teachings regarding the use of a liberated 5' portion, cleaved from a first oligonucleotide, to form a second complex with a third oligonucleotide, such that the said second complex is also cleaved by an enzyme comprising a 5' nuclease. The combination with the fluorescence methods of Higuchi does not cure this deficiency. This combination of references fails to teach or suggest the elements of the presently claimed invention and, as such, the presently claimed invention is nonobvious in view of these references. Applicants therefore respectfully request that these rejections be removed.

The Examiner makes a further combination of these references with Szybalski. Claims 71-94 stand rejected under 35 U.S.C. § 103 as being unpatentable over Goodman in view of Higuchi and Gelfand, and further in view of U.S. Patent No. 4,935,357 to Szybalski (hereinafter Szybalski). In the Office Action of 6/17/03 (page 10) the Examiner argues that “it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to modify the method of nucleic acid cleavage and nucleic acid detection by fluorescence quenching of Goodman et al., Higuchi et al. and Gelfand et al. by substituting the nucleotide “adapter” comprising a hairpin structure adjacent to a single stranded 3’ arm (adjacent to the duplex region) as taught by Szybalski.” Applicants respectfully disagree. As noted above, none of Goodman, Higuchi, or Gelfand, *either alone or in combination*, teach a method comprising the liberation of a 5’ portion of a first oligonucleotide by cleavage with an enzyme comprising a 5’ nuclease and the use of the liberated 5’ portion to form a second complex with a third oligonucleotide, wherein said second complex is also cleaved by an enzyme comprising a 5’ nuclease. The combination of Goodman, Higuchi, and Gelfand with the hairpin adapters of Szybalski fails to cure the deficiency. None of these references, alone or in combination, teach or suggest the use of the hairpin adapters in the formation of complexes that are cleaved by an enzyme comprising a 5’ nuclease.

To establish *prima facie* obviousness of a claimed invention, ***all*** the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981 (CCPA 1974). Here, Goodman, Higuchi, Gelfand, and Szybalski, whether taken alone or *in any combination*, fail to teach the presently claimed methods comprising the liberation of a 5’ portion of a first oligonucleotide by cleavage with an enzyme comprising a 5’ nuclease and the use of the liberated 5’ portion to form a second complex with a third oligonucleotide, wherein said second complex is also cleaved by an enzyme comprising a 5’ nuclease. As such, the presently claimed invention is nonobvious in view of these references and Applicants respectfully request these rejections be removed.

### **CONCLUSION**

For the reasons set forth above, it is respectfully submitted that Applicants have addressed all objections and rejections, and Applicants' claims should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this

application, Applicants encourages the Examiner to call the undersigned collect at (608) 218-6900.

Dated: March 16, 2004



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